## REMARKS

Reconsideration and withdrawal of the rejections set forth in the Office Action dated March 25, 2003 are respectfully requested.

### I. Election/Restriction

Applicants affirm election of claims 1-26 with election of SEQ ID NO:2. Claims 8 and 19 are withdrawn from consideration as drawn to a non-elected invention.

### II. Amendments

Claims 1-11, 23, and 24 stand cancelled.

Claim 12 is amended to include the limitation of claim 24, namely that the method is directed to an organ *in vivo*.

Claims 13, 15, and 17 are amended for consistency with the amendment to claim 12.

Claims 16 and 22 are amended to correct typographical errors.

Claims 25 and 26 are amended to depend from claim 12 in light of the cancellation of claims 23 and 24.

Thus, claims 12-18, 20-22, 25, and 26 remain pending for examination.

### III. Double-Patenting Rejection

Claims 1-3, 7, 11-13, 18, 22-26 were rejected under the judicially-created doctrine of obviousness-type double patenting at being unpatentable over claims 10-12 of U.S. Patent No. 6,165,977, issued December 26, 2000. The Examiner noted that a timely filed Terminal Disclaimer in compliance with 36 C.F.R. §1.321(c) would overcome an actual or provisional rejection on this ground.

Enclosed herewith is an executed Terminal Disclaimer filed in accordance with C.F.R. §1.321(b) and (c) which disclaims the terminal portion of any patent issuing on the instant application that extends beyond the expiration of U.S. Patent No. 6,165,977.

Applicants submit that the Terminal Disclaimer overcomes the rejection for obviousness-type double patenting and withdrawal of the rejection is respectfully requested.

## IV. Rejections under 35 U.S.C. § 102

Claims 1-3, 7, 9, 10, 12-14, 18, 23, and 25 were rejected under 35 U.S.C. §102(b) as allegedly anticipated by Dorn *et al.* (*PNAS*, 96(22):12798 (1999)) . This rejection is respectfully traversed for the following reason.

### A. The Present Invention Art

The present invention relates to a method of reducing injury to an organ *in vivo* exposed to an ischemic or hypoxic condition, comprising administering to the organ a ψεRACK peptide.

### B. The Cited Art

Dorn *et al.* describe delivery of a ψεRACK peptide to neonatal cardiac myocytes *in vitro*. The peptide was introduced into the cell by transient permeabilization with saponin. Dorn *et al.* also describe creation of transgenic mice that express ψεRACK specifically in cardiomyocytes.

### C. Analysis

The standard for lack of novelty, that is, for anticipation, is one of strict identity. To anticipate a claim for a patent, a single prior source must contain all its essential elements. M.P.E.P. § 2131.

An element of the present invention is 'administering to an organ *in* vivo a ψεRACK peptide'. This feature is nowhere shown by Dorn *et al.* The teaching in Dorn *et al.* is limited to (1) administration of a ψεRACK directly to a cell *in vitro* by permeabilization with saponin and (2) creation of transgenic mice that express ψεRACK peptide in cardiomyocytes. Nowhere do Dorn *et al.* show administration of ψεRACK peptide to an organ *in vivo*.

Accordingly, Applicants respectfully request withdrawal of the rejection under 35 U.S.C. §102.

## V. Rejections under 35 U.S.C. § 103

Claims 1-7, 9-18, and 20-26 were rejected under 35 U.S.C. §103 as allegedly obvious over Liang *et al.*, U.S. Patent No. 6,329,349 in view of Dorn *et al.* This rejection is respectfully traversed for the following reason.

### A. The Present Invention Art

The present invention is described above.

### B. The Cited Art

LIANG *ET AL.* describe prevention or reduction of ischemic heart damage by administration of monophosphoryl lipid A and a second organic compound.

DORN *ET AL.* is described above.

### C. Analysis: A Prima Facie Case of Obviousness Has Not Been Established Since There is No Reasonable Expectation of Success

According to the M.P.E.P. § 2143, "to establish a prima facie case of obviousness, ... there must be a reasonable expectation of success."

Delivery of peptides and polypeptides for use a therapeutic agents is known to be fraught with problems[1,2,3] (copies enclosed). Many promising new peptides have been identified, yet their clinical utility has been limited by delivery problems[1,3]. Long hydrophilic amino acid chains block transport across biological membranes; adsorption does not correlate with bioavailability; and crossing membranes can provoke denaturation or degradaion[2]. Additionally, loss of function may provoke potential

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[1]Burton, P.S. *et al.*, *J. Pharm. Sci.*, 85(12):1336 (1996) (copy enclosed).

[2]Edgington, S., *Biotechnology*, 9:1327 (1991) (copy enclosed).

[3]Juliano, R.L., *Annals of the NY Acad. Sci.*, 507:19 (1987) (copy enclosed).

immunogenicity and the peptide itself might self-up regulate or down-regulate[2,3]. The poor bioavailability of peptides is caused by metabolism of the peptide and by inefficient transport of the peptide across cell membranes[1,3].

There is no way *a priori* to know if any given peptide upon administration *in vivo* will be therapeutically effective. Certainly, if peptide delivery readily and easily provided efficacious therapy, there would be many more peptide products on the market. Unfortunately, the state of the art is not at a place where peptides are readily delivered to provide therapy.

In the present rejection, the Examiner asserts that "it would have been obvious to the person of ordinary skill in the art at the time the invention was made to use the ψεRACK peptide of Dorn *et al.* in the method of reducing ischemic injury of the heart via the sequential administration of cardioprotective agents of Liang *et al.*" That is, "it would have been obvious... to substitute one for another." (Office action, page 7, first full paragraph).

The disclosure of Liang *et al.* is limited to delivery of cardioprotective agents that are non-peptides. More specifically, Liang *et al.* describe administration of monophosphory lipid A (MLA) in combination with adenosine, agonists of the $A_1$ and $A_3$ adenosine receptors, antagonists of the $A_{2a}$ adenosine receptor, and $K_{ATP}$ channel openers (Col. 2, lines 10-25). MLA is not a peptide and the compounds that act as agonists and antagonists of adenosine receptors, shown beginning on Col. 8, are all small organic compounds. There is nothing in the teaching of Liang *et al.* that would give one of skill in the art any reason to expect that a peptide delivered *in vivo* to an organ would be therapeutically effective, for two reasons. First, Liang *et al.* does not describe therapy with any peptides. Second, even if he did, all the experiments reported in Liang *et al.* were done *in vitro* on cardiac myocytes. Based on this, there is nothing for one of skill in the art to rely on to have any expectation that selection of a peptide for "substitution" into the method of Liang *et al.* would be successful.

The teaching in Dorn *et al.* provides nothing to alleviate this problem. Dorn *et al.* is limited to a showing (1) *in vitro* administration of ψεRACK peptide to a cell by transient permeabilization; and (2) intracellular expression of ψεRACK peptide in

transgenic rodents. Nothing in Dorn *et al.* shows or suggests that the peptide could be administered to an organ *in vivo* for therapeutic activity.

Obviousness requires an expectation of success, which requires at least some degree of predictability (MPEP § 2143.03). Given the state of the art belief, today and at the time of Applicants' filing, that delivery of peptides in general is fraught with hurdles to achieve intracellular delivery for efficaceous therapy, it is incorrect to assert that mere substitution of a peptide for an organic compound in a treatment method would be obvious. There is nothing in the cited references of a ψεRACK peptide to an organ for treatment of ischemia.

Accordingly, the rejection based on a combination of Liang *et al.* and Dorn *et al.* fails to establish a *prima facie* case of obviousness, and withdrawal is respectfully requested.

## VI. Conclusion

In view of the foregoing, the claims pending in the application comply with the requirements of 35 U.S.C. § 112 and patentably define over the applied art. A Notice of Allowance is, therefore, respectfully requested. If the Examiner has any questions or believes a telephone conference would expedite prosecution of this application, the Examiner is encouraged to call the undersigned at (650) 838-4402.

Respectfully submitted,

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